Walton Centre / Clatterbridge Centre for Oncology guidelines for high grade glioma management

1 Background

High grade gliomas (HGG) account for ~70% of all gliomas and predominantly affect patients between 40-70 years of age. They are diffusely infiltrating tumours, which according to the WHO classification can be divided into anaplastic astrocytoma (WHO grade III), anaplastic oligodendrogliaoma (WHO III), anaplastic oligoastrocytoma (WHO grade III) and glioblastoma multiforme (GBM) (WHO grade IV) (4). They are commonly located in or near to eloquent brain regions, i.e. motor, language, visuo-spatial and memory. These tumours continue to have growth potential, there is no stable tumour and recurrence tends to be at the site of the original disease. More recently recurrence distant from the original site has been reported (so called multi-focal recurrence). Death is usually due to recurrence and disease progression and the optimal treatment of HGG is tailored to individual patients.

1.1 Clinical Features

Features of raised intracranial pressure and focal neurological deficit are the commonest presenting complaint. Patients may also have partial or generalised seizures and an appropriate antiepileptic drugs (AED) should be commenced. Focal neurological deficits are more likely to be permanent due to the infiltrative nature of these tumours, however in some patients these improve with dexamethasone and surgical resection.

1.2 Conventional and advanced MR imaging

High grade gliomas tend to be hypointense on T1W, with marked peripheral contrast enhancement with gadolinium. They have a heterogeneous signal on T2W and FLAIR which extends beyond the margins of the tumour seen on T1 + gadolinium. MR spectoscopy, perfusion and diffusion provide additional information at baseline assessment and can be used to differentiate gliomas from other lesions e.g. abscess, meningioma, metastasis.

1.3 Prognosis

Due to their infiltrative nature high grade gliomas are not curable. Prognosis according to pathology is: anaplastic oligodendrogliomas > anaplastic astrocytoma > glioblastoma. Anaplastic gliomas (grade III) have a median progression free survival (PFS) of ~2 years, and a median overall survival (OS) of ~3 years. Glioblastoma multiforme (GBM) has a worse prognosis and the median OS is 12-14 months, however there are an increasing number of longer term survivors, beyond 2-3 years. Radiotherapy with concomitant and adjuvant temozolomide (Stupp regime) is now the gold standard regime for GBM and increases median OS from 12.1 to 14.6 months, and increases 2 year survival from 10.4% to 26.5% (6). Age, performance status, extent of surgical resection, mini mental score examination (MMSE) and MGMT status are significant prognostic factors and the EORTC produced an online calculator that can be used to estimate prognosis for individual patients.
2. Management options

2.1 Surgery
Surgical options include biopsy, debulking and macroscopic resection, which provides tissue for diagnosis, grading, molecular studies and ongoing research. Surgical options depend on clinical condition, performance status, tumour location, response to dexamethasone and patient choice. The aim of gross total resection (GTR) is removal of all the contrast enhancing tumour visible on MRI T1+gadolinium. In addition to providing a diagnosis, GTR and tumour debulking (subtotal resection: STR) reduce the mass effect, reduce the dexamethasone requirement and may improve neurology and performance status. The effect of extent of resection (EOR) on OS and PFS is increasingly being recognised to improve prognosis and subsequent response to adjuvant therapy.

Intra-tumoural carmustine wafers (Gliadel) are a surgical adjunct, which are NICE approved for first line treatment of HGG. Wafers are placed in the resection cavity (>90% resection should be achieved) and the chemotherapy diffuses 2-3 mm into the tumour bed. The offer a modest increase in median OS of ~2 months (1).

Fluorescence-guided resection (Gliolan) is a new technology that produces detectable fluorescence within the tumour at resection and has been demonstrated to increase the extent of resection, and therefore median OS (5).

2.2 Radiotherapy
Adjuvant external beam fractionated radiotherapy aims to prolonged time to inevitable tumour recurrence and progression, whilst minimising CNS adverse effects such as radiation necrosis and neuro-toxicity leading to cognitive decline. Three radiotherapy regimes are in common use and are tailored to individual patients:

a) radical radiotherapy with concomitant temozolomide (Stupp regime) (6)

b) radical radiotherapy alone

c) palliative radiotherapy

2.3 Chemotherapy
Temozolomide is the chemotherapy drug of choice and in certain patients is given concomitantly with radiotherapy followed by 6 cycles of adjuvant treatment as part of the Stupp regime (6). CCNU is less effective and is typically used when there is evidence of tumour recurrence or progression, when there are no further surgical options.
2.4 **Best supportive treatment / palliative care**

At initial presentation some patients are not fit enough for adjuvant radiotherapy, therefore biopsy for tissue diagnosis is not indicated and symptomatic treatment only should be offered. This assumes that the MRI appearance of the tumour is consistent with a diagnosis of HGG. In addition, following surgery, some patients do not recover or improve sufficiently to have adjuvant radiotherapy and symptomatic treatment only should be offered.

2.5 **Treatment options at recurrence**

High grade gliomas all tend to recur and treatment is tailored to individual patients according to clinical status, radiological pattern of recurrence and following MDT discussion. Options include:

a) revision surgery +/- Gliadel
b) revision surgery +/- further radiotherapy
c) 2nd line chemotherapy with CCNU
d) re-challenge chemotherapy with temozolomide
e) stereotactic radiosurgery (SRS) in highly selected cases
f) participation in clinical trials

3. **WCFT / COO management guidelines (see flowchart)**

3.1 **At presentation**

- Baseline conventional MRI brain
- Patient discussed pre-operatively at neuroscience MDT
- Commence AED if patient has seizures – consider neurology advice / input if refractory
- Discuss management aims: maintain quality of life, minimise tumour volume, stabilise disease
- Discuss management options:
  - Best supportive treatment / palliative care
  - Biopsy
  - Resection (GTR, STR)

- It is important to emphasis that these tumours are malignant and not curable

3.2 **Surgery**

- Surgical resection should be the first treatment option – the goal is maximal safe resection of signal abnormality defined on T1+gad. The post-operative MRI should be obtained within 72 hours and include a volume T1+gad to determine EOR and volume of residual disease as per the RANO criteria for measuring response to treatment (7).
- Awake craniotomy +/- neurophysiology monitoring should be considered for eloquent tumours
• When resection is not feasible due to location / extension / co-morbidity / patient choice biopsy for histological conformation should be obtained
• Re-resection should be considered at recurrence according to clinical status, initial response to treatment and radiological appearance
• Gliadel is currently reserved for patients aged ≤50 years old who have surgically respectable recurrent tumour > 6 months following completion of radiotherapy for HGG (both grade III and IV)
• Gliolan is currently only available to patients enrolled in the GALA-5 clinical trial (WCFT is an approved investigating site)

3.3 Radiotherapy
• Stupp regime is offered to patients <70 years old and performance status 0 -1
• Radical radiotherapy is offered to patients >70 years old and performance status 0 -1
• Palliative radiotherapy is offered to patients of performance status 2

3.4 Chemotherapy
• Temozolomide is given as part of Stupp regime and as a re-challenge at recurrence
• CCNU is 2nd line chemotherapy used at recurrence

3.5 Clinical and radiological follow-up
To minimise duplication of clinic appointments and MRI scans the following is proposed:
• MRI is the modality of choice for follow up and should include T1 +/- gad, T2, FLAIR
• MRI schedule and location:
  o Pre-surgery – WCFT / referring hospital as per radiology CNG agreement
  o Post-surgery (within 72 hours only in those undergoing GTR or STR) - WCFT
    Pre-RT planning - CCO
    Post-RT (1 month post-RT, pre-adjuvant chemo) - CCO
    Mid-adjuvant chemo (after 3 cycles) - CCO
    Post-adjuvant chemo (after 6 cycles) - CCO
    Every 6 months from 12 months-24 months - CCO
    Any routine MRI images after 24 months - CCO / Walton
• Perfusion MRI can be useful for differentiating between tumour recurrence, pseudoprogression and radiation necrosis – this can be performed at WCFT
• Clinical follow-up during radiotherapy is by the clinical oncologist
• Follow up after completion of radiotherapy can be by the oncologist and / or neurosurgeon either alone, in conjunction or alternatively. All effort should be made to avoid duplication of OPD and MRI attendances
• Patients undergoing further surgery +/- Gliadel at recurrence should be follow-up by the neurosurgeons until recurrence then transferred back to the clinical oncologist for possible chemotherapy

• Once all active treatment options have been exhausted follow-up should be transferred to palliative care team

4. References


New radiological diagnosis of high grade glioma
• Baseline MRI
• Consent for tumour bank
• Options: biopsy, resection, palliative

Seizures?
Yes
Start AED
No
No role for prophylactic AED

Diagnosis
• GBM
  ▪ ECOG 0-1
  ▪ Age < 70

Adjuvant options
• Radiotherapy only: Radical or palliative
• Chemoradiotherapy
  ▪ XRT + temozolomide

Adjunct options
• Radiotherapy
• Biopsy
  ▪ For gliomatosis
  ▪ Patient choice

Surgical options
• Gross total resection (GTR)
• Subtotal resection (STR)
  ▪ Post-op MRI within 72 hours to assess EOR
  ▪ Neurophysiology monitoring and awake craniotomy for eloquent tumours

Fluorescence (Gliolan) – guided resection for tumours amenable to GTR

Follow-up
• Neurosurgery / neuro-oncology clinic
  MRI follow-up

Occurrence
• Anaplastic astrocytoma
• Anaplastic oligodendrogial

Palliative
• Best supportive treatment
• Palliative care team input

The Liverpool high grade glioma pathway